A population-based study of the impact of dialysis on mortality in multiple myeloma

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Title: The impact of dialysis on mortality in multiple myeloma

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Summary

Background Severe acute kidney injury requiring in-hospital dialysis is a major complication of multiple myeloma (MM). However, patients with this complication have been excluded from clinical trials, and studies on mortality predate current chemotherapy regimens and were not population-based.

Methods We utilised National Health Service and Office of National Statistics data to study 36,348 patients in England with a first diagnosis of MM between April 1, 2006 and March 31, 2014, of whom 1,240 (3·4%) had a first in-hospital dialysis treatment within 28 days of diagnosis. Patient demographics included age, gender, ethnicity, and area socio-economic deprivation. The primary endpoint was mortality.

Findings Overall median survival was 3·0 years (interquartile range [IQR] 0·7-8·1). Kaplan-Meier analysis showed that patients who did not receive dialysis had a median survival of 3·0 years (IQR 0·7-8·2) and patients who received dialysis had a median survival of 1·4 years (IQR: 0·2-4·6). From 2006/7 to 2010/11 survival improved from 2·6 years (IQR 0·6-7·7) to 3·3 years (IQR 1·0-not reached) for patients who did not receive dialysis and 0·6 years (IQR 0·1-2·7) to 1·2 years (IQR 0·4-4·0) for those patients who received dialysis. This improvement was greater in patients that received dialysis (hazard ratio [HR] 2·89 (95% confidence interval [CI] 1·96, 4·24; P<0·001) in 2006/07 vs 1·00 in 2013/14) compared to those that did not (HR 1·49 in 2006/07 [CI 1·40, 1·59; P<0·001) vs 1·00 in 2013/14). Cox regression analysis showed that those who received dialysis were more likely to be older, male and more socio-economically deprived.

Interpretation Dialysis is a strong independent risk factor for increased mortality in patients with MM. Whilst the survival of patients who receive dialysis has substantially improved since 2006/7, in 2013/14 this group of patients still had a median survival less than half that of patients who did not receive dialysis treatment.

Funding None

Introduction

There are no contemporary population-based data available on the impact of dialysis on the survival of patients with multiple myeloma (MM). This is an important evidence gap as acute kidney injury in patients with MM is common. Up to 50% of patients with MM have renal impairment at presentation; around 10% of which require dialysis for severe acute kidney injury (AKI) usually secondary to myeloma cast nephropathy, a direct consequence of immunoglobulin light chain paraprotein.[1-3] Over the past decade advances in chemotherapy have led to earlier disease responses as measured by circulating paraprotein levels,[4] however the impact of this development on the survival of patients with MM who require dialysis is uncertain.

Single centre and registry studies that predate current chemotherapy regimens report median overall survival of less than one year in patients with dialysis-dependent renal failure.[5,6] In contrast, overall survival for patients with MM in randomised controlled trials is now over four years,[7,8] with significant improvements in the past decade associated with advances in chemotherapy.[9] Patients with severe AKI have been excluded from randomised controlled trials of chemotherapy in MM, so it is not known if these new treatments are leading to better long-term survival in patients who require dialysis.

The Greek Myeloma Study group recently reported renal function data on 1,773 consecutive patients who were treated for MM from 1990 and showed that 18% of patients had severe renal impairment at presentation as defined by an estimated glomerular filtration rate (eGFR) <30 ml/min/1·73m^2.[10] Since 2005, 3·5% of the patients reported in this study required dialysis treatment. An eGFR of <30 ml/min/1·73m^2 at initiation of treatment for MM was independently associated with a worse survival.

The lack of population-based outcome data for patients with MM who require dialysis treatment is important as understanding the impact of dialysis on outcome will both help target treatment, including prioritising the inclusion of patients who have severe AKI in clinical trials, and provide prognostic information for patients and health-care professionals.

To address this, we extracted data for all patients treated in the National Health Service (NHS) in England between April 2006 and March 2014 with a first coded diagnosis of MM and a first coded diagnosis of dialysis received in a hospital within 28 days of a diagnosis of MM. The aim of this study was to identify the impact of dialysis on survival of patients with MM and report trends in survival since the introduction of novel chemotherapy regimens.

Methods

We obtained data on all patients with a new diagnosis of MM in England between April 1, 2006 and March 31, 2014. Data were obtained from Hospital Episodes Statistics (HES), an administrative data warehouse containing all NHS funded admissions to hospitals in England. It contains detailed records relating to individual patient diagnoses and treatment, with data extraction facilitated by using codes on procedural classifications (Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th revision [OPCS-4] and medical classifications (World Health Organization International Classification of Disease, 10th revision [ICD-10]). Patient demographics obtained at the time of diagnosis included age, gender, ethnicity, Charlson co-morbidity score, and area socio-economic deprivation. To avoid confounding by the two variables of interest, kidney disease and tumour were excluded from the Charlson co-morbidity score calculation.

This study included all patients with a new diagnosis of MM (ICD-10 code C900), a first code associated with a dialysis treatment was also extracted (OPCS-4 codes X401, X402, X403, X405, X406, ICD10 codes Z992, Z491, Z492). With regard to outcome analysis, HES data alone have the limitation of only capturing deaths occurring in a hospital setting. To obtain a complete mortality data, the study cohort was cross-referenced with mortality data from the Office for National Statistics, which collects information on all registered deaths in England and Wales. Combining sources via this data linkage process created a

comprehensive dataset with regard to mortality, which was the end point of interest in this analysis. This study did not require institutional review board approval owing to the pseudo-anonymised nature of the data retrieved; data were linked by NHS Informatics using a special HES identity code and avoided patient-identifiable codes.
Determination of socio-economic deprivation was based upon the Index of Multiple Deprivation (2010), a multiple deprivation model calculated at the local-level area. The model is based upon assessment of distinct domains of deprivation that can be individually recognized and measured.

Statistical methods
The primary study outcome was death after a new diagnosis of MM stratified by the presence or absence of first dialysis within 28 days of diagnosis of MM. STATA (v 13·1 College Station, TX: StataCorp LP) was utilized for data analysis. Categorical variables are presented as number (%) and continuous variables as mean (± standard deviation (SD)) or median (interquartile range (IQR)) dependent on normality of distribution. Difference between groups was assessed with χ^2 or two-sided Fisher's exact test for categorical variables. A *P*-value <0·05 and 0·001 in the statistical analysis was considered significant and highly significant, respectively.
Kaplan- Meier curves were produced to assess survival, and log- rank test used to assess any differences in survival. Cox's regression model using the command stcox was utilized. The proportionality assumption was checked for each variable and the whole model. For the main analysis, the proportionality assumption is true for all variables except cancer. Variables included in the model were age, gender, ethnicity, socio-economic deprivation, ethnicity, year of diagnosis, and Charlson co-morbidity score.
With the assumption that data was missing at random, we performed list-wise deletion and excluded the missing values from the analysis. Other missing data (e.g. ethnicity) was adjusted for as dummy variables in the models as required.

Data accuracy
The study based on the following assumptions: (i) that all patients with a first diagnosis of MM in England had a code consistent with a diagnosis of MM entered; (ii) that all patients with a first diagnosis of MM who required dialysis did so within 28 days of that diagnosis at a hospital unit. The overall diagnostic and procedural accuracy of England and Wales HES data is reported as around 90% for primary diagnosis and procedural codes.[11]
It is unknown how many patients with MM and severe AKI requiring dialysis received dialysis at a community (satellite) dialysis unit rather than a hospital based dialysis unit, as coding data for those patients are not collected in HES. However, due to the nature of the presentation of AKI and MM, the likelihood of receiving dialysis in a satellite dialysis unit only within 28 days of the diagnosis of MM in England is very low.
The only large dataset that has been published on the requirement for dialysis at the time of diagnosis is from the Greek Registry, which reported that 3·5% of patients with a new diagnosis of MM required dialysis at presentation.[10] This report is comparable with the figures that are reported in this current study.

Role of the funding source

The study was not supported by any external funding or sponsorship. FE and DR had access to the raw data. PC had full access to all the aggregate data and the final responsibility to submit the full application

Results

36,348 patients were recorded in the HES data with a new diagnosis of MM between April 2006 and March 2014. Of these patients, 1,240 (3·4%) had a first in-hospital dialysis treatment within 28 days of this diagnosis. Median patient follow-up was 4·4 years (IQR 2.6-6.5).

Table 1 shows the baseline characteristics of the study cohort. The median age for the whole cohort was 73 years (IQR 63-80). 20,167 (55·4%) were men and 16,181 (44·5%) were women. Ethnicity comprised 29,593 (81·4%) White, 1,459 (4·0%) Black or Black British, 947 (2·6%) Asian or Asian British, 565 (1·6%) other, and 3,784 (10·4%) unknown. The patient numbers by socio-economic deprivation quintiles were (from most to least deprived, respectively): one, 5,967 (16·4%); two, 6,600 (18·2%); three, 7,527 (20·7%); four, 7,955 (21·9%); and five, 8,105 (22·3%). Co-morbidity quantified by Charlson score showed: 25,142 (69·2%) patients had a score of 0; 3,475 (9·5%) a score of 1-4; 7,731 (21·2%) a score of 5 or more. The numbers diagnosed with MM increased by year from 3,993 in 2006/7 to 5,068 in 2013/14. The percentage of patients treated with dialysis increased from 3·16% in 2006/7 to 3·86% in 2013/2014.

Patients who received dialysis were more likely than those who did not receive dialysis treatment to have been over 70 years old, of male gender, to have had more deprived socio-economic deprivation quintile, and have had a higher Charlson score. There was no significant difference in ethnic group prevalence between patients who required and did not require dialysis treatment.

Survival analysis

Overall median survival was 3·0 years (IQR 0·7-8·2), there was no difference in survival when stratified for gender. Kaplan-Meier survival analysis was performed to assess the unadjusted difference in risk of death between patients with a diagnosis of MM by whether or not they received dialysis treatment. Figure 1 shows the overall survival by dialysis vs non-dialysis. Median survival was 3·0 years (IQR 0·7-8·2) in the non-dialysis group compared to 1·4 years (IQR 0·2-4·6) in the dialysis group.

Survival by year of diagnosis

Figure 2 shows survival by year of diagnosis. There was a progressive improvement in survival over the study period. Figure 2a shows survival by year of diagnosis in patients who did not receive dialysis treatment, with median survival increasing (not significantly) from 2·3 years (IQR 0·4-6·9) in 2006 to 3·2 years in 2010 (IQR 0·8-4·1). Figure 2b shows outcomes in patients who received in-hospital dialysis. Median survival improved from 0·6 years (IQR 0·1-2·5) in 2006/07 to 1·2 years (IQR 0·2–3·7) in 2010/11. Table 2 shows the relative risk of death by year of diagnosis for patients in the study.

Cox regression model

Table 2a shows results of the patients with a coded diagnosis of MM regardless of whether or not they received dialysis. There was an independent association with an increased hazard ratio (HR) of death by increased age, more socio-economically deprived quintile, year of diagnosis, and Charlson score and with a decreased HR of death by gender (female vs male) and ethnicity (non-white vs white). Table 2b and table 2c show results for patients with a coded diagnosis of receiving and not receiving dialysis respectively. For patients with a coded diagnosis of receiving dialysis, there was an increased HR for death by age, Charlson score of 5+, and year of diagnosis, but not by deprivation index. There was a decreased HR of death for ethnicity (lower HR for black vs white). For patients not receiving dialysis, there were the similar associations to those presented in table 2a.

Discussion

Outcomes for patients with MM who required dialysis treatment in the past decade have not been previously reported. This is an important shortfall as there has been a significant improvement in survival in patients with MM in this period. Recent randomised controlled trials for the treatment of newly diagnosed myeloma have reported overall median survival in excess of four-years.[7,8,12,13] However, all large intervention studies of MM patients to date have excluded those who require dialysis or have an eGFR of less than 15 ml/min/1·73m^2.

In this study we show that between 2006/7 and 2013/14, patients with MM who required dialysis at presentation had an increased mortality compared to patients who did not require dialysis. This effect was independent of age, gender, ethnicity and year of diagnosis. Other independent factors associated with an increased mortality risk in patients with MM included age, gender, socio-economic deprivation and Charlson score.

This study indicates that the improvement in survival for patients with MM who fulfilled inclusion criteria for major clinical trials also occurred in patients who, as a consequence of requiring dialysis, would have been excluded from these trials. The median overall survival of patients with MM who required dialysis at presentation, improved from 7 months in 2006/07 to 17 months in 2013/14. In multivariable analyses, with adjustment for patient demographics including age and ethnicity, this trend remained significant, with an almost three-times lower risk of death in the most recent time cohort compared to 2006/07. In those patients that did not receive dialysis, mortality also improved with time in the Cox regression model. Interestingly the magnitude of this effect was smaller compared to dialysed patients, with a 1·5 fold lower risk of death in 2013/14 compared to 2006/07.

The understanding that severe renal impairment in patients with MM is a major determinant of increased mortality was derived from studies that pre-date current chemotherapy regimes. A single centre study of 88 consecutive patients who presented between 1998 and 2005 with MM and required dialysis reported a median survival of 10·2 months.[5] This was consistent with European registry data, which reported that patients with a coded diagnosis of MM or light chain deposition disease and dialysis between 1986 and 2005 had an overall survival of less than one-year from starting dialysis treatment.[6] The population-based

survival for 2006/7 that we report in this present study is consistent with these reports.

In the past decade, since the widespread adoption of novel chemotherapy regimes, both single centre and pooled analyses indicate that patients who require dialysis may be surviving longer.[14-17] However, until this present study, it has been uncertain whether these observations from specialist centres with a clinical interest in MM and severe renal failure are generalizable. In addition to the use of chemotherapy regimens, the interventions that are being reported from single centres are multifactorial, including fast-tracking diagnosis and commencement of treatment and use of more efficient extra-corporeal light chain removal technology.[15,16]

This systematic omission from clinical trials of patients with MM and severe renal impairment may be due both to uncertainties of the safety profile of novel chemotherapy agents in severe renal impairment and the complexity of care required for patients with co-incident renal failure requiring life-preserving organ support therapy (dialysis treatment). The improvement in outcomes may relate in part to the introduction of novel agents into routine clinical practice for these patients during the last decade, based in part on the pragmatic and widely implemented recommendation from the International Myeloma Working Group in 2010 for the use of bortezomib with high-dose dexamethasone for patients with MM and AKI.[18] For patients with MM and renal impairment there is accumulating evidence that bortezomib is contributing to better overall survival,[19] and multicentre trials are now recruiting patients with MM and utilising bortezomib-based chemotherapy regimens. [20,21]

There are limitations to our study. Foremost we are bounded by the accuracy of the HES data warehouse from which our dataset has been constructed. In this study we have utilised routinely coded clinical information for the identification of two diagnoses that require coding based identification for the purposes of remuneration of the health-care provider (the payment by results system [PBR]). NHS trusts have utilised this system since 2006/7. Data coding inaccuracies in diagnosis (ICD-10) and procedure (OPCS-4) codes are penalised financially and investigated by the UK Care Quality Commission which mandates yearly audit of data accuracy. Both diagnostic and procedure coding using HES data has been estimated to be approaching 90%. [11]

By utilising one or more codes associated with MM and one or more codes associated with dialysis we were able to calculate the incidence of MM and from that ascertain that the incidence of patients who present with dialysis-dependent kidney disease associated with MM is consistent with other population-based studies. One potential shortfall of the study is the assumption that patients with a first coded diagnosis of MM who develop end stage renal failure requiring dialysis must have received at least one treatment in a hospital based dialysis unit, rather than a community (satellite) based dialysis unit. MM and severe AKI requiring dialysis treatment is a medical emergency that usually requires in-patient care. This present study has found that around 3·4% of MM patients were dialysed within 28 days of presentation and this is in good agreement with the largest contemporary multicentre trial.[10]

This present work has evaluated the mortality patients with a new diagnosis of MM and of dialysis-dependent renal failure. However there remain a number of important outstanding clinical research questions. One interesting aspect relates

to the relatively wide variation in survival amongst dialysed MM patients that we report. Some of the clinical heterogeneity in this group may relate to the relationship between early reductions in the serum immunoglobulin light chain levels and recovery of independent kidney function.[22-24] Early identification of patients who are at a high risk of not recovering from dialysis, based on slow serum immunoglobulin light chain reduction, may encourage studies designed to test the efficacy of early changes in chemotherapy in this group. [25]

In conclusion, this population-based study shows that the survival of patients with new diagnosis of MM requiring dialysis improved between the years 2006/7 and 2013/14. However the HR for death associated with MM remains significantly worse when associated with a requirement for in-hospital dialysis compared to patients who do not require dialysis; therefore this group of patients requires a systematic focus on the management strategies required to further improve survival.

Author contributions

The study was conceived by PC, MC, JS and PY. The study was designed by FE, DR, JS, PC and AS. MD, YA, and JP and AS reviewed the design of the study and helped identify relevant published work. FE and JS carried out the data acquisition and statistical analyses. FE, JS, PY and PC produced the figures and tables. All authors interpreted the findings and contributed to the interpretation of the findings. PC, JS, FE and PY drafted the paper, which was reviewed and modified by all authors over a number of versions. All authors saw and approved the final version. PC, DR and MC are guarantors.

Conflict of interest

Paul Cockwell has received funding for research in myeloma and kidney disease from Janssen, Baxter-Gambro and the Binding Site. Mark Cook has received received funding for research in myeloma from Janssen, Celgene Baxter-Gambro and the Binding Site. Paul Cockwell has received honoraria from Jansenn. Mark Cook has received Honoraria from Janssen and Celgene.

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Table 1. Baseline characteristics of patients with multiple myeloma (MM)

Variable	First diagnosis of MM (%)	First diagnosis of MM and a first recorded dialysis treatment within 28 days (%)	First diagnosis of MM and no recorded dialysis treatment within 28 days	P-value
Number	36,348	1,240	35,108	
Gender				
Male	20167 (55.48)	769 (62.02)	19398 (55.25)	<0.001
Female	16181 (44.52)	471 (37.98)	15710 (44.75)	
Age Group				
18-49	2131 (5.86)	62 (5.00)	2069 (5.89)	
50-59	4150 (11.42)	147 (11.85)	4003 (11.40)	
60-69	8567 (23.57)	336 (27.10)	8231 (23.44)	
70-79	11571 (31.83)	447 (36.05)	11124 (31.69)	<0.001
80+	9929 (27.32)	248 (20.00)	9681 (27.57)	
Ethnicity				
White	29593 (81.42)	971 (78.31)	28622 (81.53)	
Black/Black British	1459 (4.01)	60 (4.84)	1399 (3.98)	
Asian/Asian British	947 (2.61)	38 (3.06)	909 (2.59)	
Other	565 (1.55)	21 (1.69)	544 (1.55)	0.078
Unknown	3784 (10.41)	150 (12.10)	3634 (10.35)	
Socio-economic deprivation				
1 (most deprived)	5967 (16.42)	238 (19.19)	5729 (16.32)	
2	6600 (18.16)	238 (19.19)	6362 (18.12)	
3	7527 (20.71)	250 (20.16)	7277 (20.73)	
4	7955 (21.89)	267 (21.53)	7688 (21.90)	0.027
5 (least deprived)	8105 (22.30)	244 (19.68)	7861 (22.39)	
Charlson score				
0	25142 (69.17)	594 (47.90)	24548 (69.92)	0.001
1-4	3475 (9.56)	129 (10.40)	3346 (9.53)	
5+	7731 (21.27)	517 (41.69)	7214 (20.55)	
Year of diagnosis				
2006/07	3993 (10.99)	126 (10.16)	3867 (11.01)	
2007/08	4238 (11.66)	129 (10.40)	4109 (11.70)	
2008/09	4390 (12.08)	169 (13.63)	4221 (12.02)	
2009/10	4438 (12.21)	162 (13.06)	4276 (12.18)	<0.001
2010/11	4648 (12.79)	163 (13.15)	4485 (12.77)	
2011/12	4707 (12.95)	202 (16.29)	4505 (12.83)	
2012/13	4866 (13.39)	188 (15.16)	4678 (13.32)	

Abbreviation: IMD, index of multiple deprivation

Table 2a: Cox regression model all patients

Variable	Hazard ratio (confidence interval)	P-value
Female vs Male	0.95 (0.93, 0.98)	0.001
Age Group		
18-49	1 (reference cat)	
50-59	1.31 (1.19, 1.44)	<0.001
60-69	1.77 (1.62, 1.93)	<0.001
70-79	2.89 (2.65, 3.15)	<0.001
80+	5.20 (4.77, 5.67)	<0.001
Ethnicity		
White	1 (reference cat)	
Asian	0.73 (0.66, 0.80)	<0.001
Black	0.70 (0.64, 0.76)	<0.001
Other	0.67 (0.59, 0.76)	<0.001
Unknown	0.92 (0.88, 0.97)	<0.001
Socio-economic quintile		
1 (most deprived)	1.21 (1.16, 1.27)	<0.001
2	1.10 (1.06, 1.15)	<0.001
3	1.05 (1.01, 1.10)	0.016
4	1.05 (1.01, 1.09)	0.022
5 (least deprived)	1 (reference cat)	
Charlson score		
0	1 (reference cat)	
1-4	1.23 (1.18, 1.30)	<0.001
5+	1.75 (1.70, 1.81)	<0.001
Financial year		
2006/07	1.53 (1.44, 1.63)	<0.001
2007/08	1.44 (1.36, 1.54)	<0.001
2008/09	1.36 (1.28, 1.44)	<0.001
2009/10	1.28 (1.20, 1.36)	<0.001
2010/11	1.22(1.15, 1.19)	<0.001
2011/12	1.11 (1.04, 1.19)	0.001
2012/13	1.06 (0.99, 1.13)	0.092
2013/14	1 (reference cat)	

Table 2b. Cox regression model for patients who received dialysis within 28 days

Variable	Hazard ratio (confidence interval)	P-value
Female vs Male	1.04 (0.90, 1.19)	0.595
Age Group		
18-49	1 (reference cat)	
50-59	1.25 (0.83, 1.90)	0.281
60-69	1.66 (1.14, 2.42)	0.009
70-79	2.22 (1.53, 3.20)	<0.001
80+	3.32 (2.27, 4.87)	<0.001
Ethnicity		
White	1 (reference cat)	
Asian	0.87 (0.59, 1.28)	0.470
Black	0.54 (0.37, 0.77)	0.001
Other	0.79 (0.47, 1.34)	0.390
Unknown	1.10 (0.90, 1.35)	0.337
Socio-economic quintile		
1 (most deprived)	1.11 (0.89, 1.38)	0.372
2	1.05 (0.85, 1.31)	0.637
3	1.05 (0.85, 1.30)	0.664
4	1.09 (0.88, 1.35)	0.408
5 (least deprived)	1 (reference cat)	
Charlson score		
0	1 (reference cat)	
1-4	1.17 (0.93, 1.48)	0.187
5+	1.25 (1.08, 1.44)	0.003
Financial year		
2006/07	2.89 (1.96, 4.24)	<0.001
2007/08	2.25 (1.53, 3.32)	<0.001
2008/09	2.38 (1.64, 3.46)	<0.001
2009/10	1.84 (1.25, 2.69)	<0.001
2010/11	1.95(1.34, 2.85)	0.001
2011/12	1.56 (1.07, 2.27)	0.022
2012/13	1.42 (0.97, 2.10)	0.074
2013/14	1 (reference cat)	

Table 2c. Cox regression model for patients who did not receive dialysis within 28 days

Variable	Hazard ratio (confidence interval)	P-value
Female vs Male	0.95 (0.93, 0.98)	0.001
Age Group		
18-49	1 (reference cat)	
50-59	1.31 (1.19, 1.45)	<0.001
60-69	1.77 (1.62, 1.94)	<0.001
70-79	2.93 (2.69, 3.20)	<0.001
80+	5.34 (4.89, 5.83)	<0.001
Ethnicity		
White	1 (reference cat)	
Asian	0.72 (0.65, 0.79)	<0.001
Black	0.71 (0.65, 0.77)	<0.001
Other	0.66 (0.58, 0.76)	<0.001
Unknown	0.91 (0.87, 0.95)	<0.001
Socio-economic quintile		
1 (most deprived)	1.21 (1.16, 1.27)	<0.001
2	1.10 (1.06, 1.15)	<0.001
3	1.05 (1.01, 1.10)	0.017
4	1.05 (1.00, 1.09)	0.032
5 (least deprived)	1 (reference cat)	
Charlson score		
0	1 (reference cat)	
1-4	1.22 (1.17, 1.29)	<0.001
5+	1.75 (1.69, 1.81)	<0.001
Financial year		
2006/07	1.49 (1.40, 1.59)	<0.001
2007/08	1.42 (1.33, 1.51)	<0.001
2008/09	1.32 (1.24, 1.41)	<0.001
2009/10	1.26 (1.18, 1.34)	<0.001
2010/11	1.20 (1.12, 1.28)	<0.001
2011/12	1.10 (1.02, 1.17)	0.008
2012/13	1.04 (0.97, 1.12)	0.229
2013/14	1 (reference cat)	